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*TITLE: A Double Blind Trial of Divalproex Sodium for Affective
Lability and Alcohol Use Following Traumatic Brain Injury*

PRINCIPAL INVESTIGATOR: Thomas P. Beresford, M.D.

CONTRACTING ORGANIZATION: Denver Research Institute
Denver, CO 80220

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14. ABSTRACT A large and under-recognized sub-set of patients suffer from both traumatic brain injury (TBI) and alcohol abuse/dependence (AA/D). This group appears to use alcohol to self-treat fronto-limbic disinhibition, expressed clinically as affective lability, following TBI. This often results in AA/D and worsens TBI prognosis. The primary study hypothesis states that symptom frequencies of fronto-limbic disinhibition, expressed as affective lability, will decrease significantly in TBI subjects treated with divalproex sodium, a mood stabilizing medication, as compared to placebo. To test the primary hypothesis, we propose an 8 week, double-blind, randomized, controlled trial comparing divalproex sodium to placebo in 50 subjects--25 per group--who suffer from both TBI and AA/D. Subjects will be recruited through the initiating site located at the Department of Veterans Affairs Medical Center, Denver. Final approval from multiple review bodies was granted on September 15, 2009. Active subject recruitment continues. There are no results to report at this time.				
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Introduction

Traumatic brain injury (TBI) is highly prevalent in at risk occupations including US service personnel. Of particular concern now are those wounded in combat in Iraq and Afghanistan where TBI appears to account for a larger proportion of casualties than in prior U.S. wars. Reports from Operation Iraqi Freedom (OIF) suggest that as many as one-quarter of personnel injured in combat there suffer TBI. (Okie, 2005) Psychiatric and neurocognitive disorders—especially disorders of mood--have been noted in as many as three-quarters of combatants who suffered TBI in previous conflicts (Lishman, 1973) and are often more adversely affected by emotional problems than by physical disabilities. (Nelson et al., 1998) Although specific data are not at hand, published frequencies suggest that as many as one combat related case of TBI in every five may likely exhibit symptoms related to fronto-limbic disinhibition that is expressed as a poorly controlled, or labile, affect. It is that condition that caught our clinical interest and led to a preliminary research project.

Specifically, the Principal Investigator (PI) observed a clinical population of former service personnel who served in high risk environments such as paratroop units, flight crews, and below decks aboard ship and who had suffered TBI. Common to all was a poorly managed affective irritability or anxiety that began after TBI and was often misdiagnosed as another Axis I psychiatric disorder, usually a mood disorder such as bipolar illness, or schizoaffective illness. Likewise, all of the cases had no such symptoms prior to TBI. This posed a clinical question: How to treat post-TBI affective lability/ fronto-limbic disinhibition?

As a class of agents, anticonvulsant medication appears, empirically, to lessen the affective lability in TBI. Carbamazepine may ameliorate agitation and disinhibited behavior as well as depression and manic symptoms following TBI. (Azouvi et al., 1999; Bakchine et al., 1989; Perino et al., 2001) Valproate may improve post-TBI aggressive behaviors (Wroblewski et al., 1997), episodic explosiveness (Geraciotti, 1994), and bipolar syndrome. (Pope et al., 1988) Affective lability may include poorly controlled expression of mood and anxiety upset. (Arciniegas and Silver, 2001) Other agents, such as benzodiazepines may address similar symptoms, yet these drugs introduce addiction and tolerance issues and do not appear to address specific causes of affective lability.

To complicate matters clinically, the PI saw many cases in the veteran population in which TBI patients had been trying to self-treat their affectively lability—generally an irritability or anxiety state that interrupted or prevented normal functioning at work or in family life, often leading to broken marriages, job losses, occasionally to homelessness. Unfortunately, the most readily available drug of choice for many TBI victims was often ethyl alcohol. The result of self treatment was frequently the development of an alcohol use disorder that only served to worsen the fronto-limbic disinhibition following the TBI.

Alcohol abuse and/or dependence (AA/D) and mood disturbance often co-occur following TBI. (Corrigan, 1995) In a group of 20 TBI survivors who had evidence of alcohol abuse in the year following their injury, 15 (75%) developed a mood disorder. (Jorge and Robinson, 2002) In a non-alcohol abusing group, only 44% patients developed a mood disorder during the same time period. (Jorge and Robinson, 2002) In persons with AA/D and affective lability following TBI, successful treatment of mood lability may reduce or eliminate drinking behaviors. (Beresford et al., 2005) Following our interests in both alcoholism and TBI, we have accrued clinical experience in recognizing and treating patients who present with mood lability including symptoms of AA/D after TBI. We have observed a similar pattern of decrease in, or cessation of alcohol use following treatment of underlying TBI-induced affective lability. Many AA/D+TBI patients describe their emotional symptoms as contributing to their heavy alcohol

use. Observed clinically, when such cases reach alcohol abstinence, their symptoms of poorly regulated affective expression most often do not appear to be those of an idiopathic mood or anxiety disorder. They do not present the severity or the same natural courses as do Major Depressive Disorder, Bipolar Illness, or Anxiety Disorder, for example. Instead both symptoms and course appear more characteristic of the sustained affective lability often observed following TBI. (Beresford et al., 2005) This suggests that TBI survivors represent a patient group for whom treatment of neuropsychiatric symptoms following TBI may alleviate both TBI-related affective lability and also heavy ethanol use by treating the condition for which ethanol is used.

We believe our clinical observation of excessive alcohol use following TBI and the response to non-blinded, open-label treatment with anticonvulsant medications are concordant with the notion of neuronal inhibition, if noted in the absence of a clearly controlling mechanism of action. From a scientific viewpoint however, the treatment of fronto-limbic disinhibited patients has been neither blinded nor placebo-controlled to this point. As such, we can only provide an interesting observation of what appears to be a beneficial treatment response to anticonvulsant medication among patients with affective lability and AA/D following TBI. This indicates the need for a more systematic investigation of this phenomenon that, if substantiated, might improve the outcome and treatment choices for those patients who suffer from both TBI and AA/D. Further investigation requires us to focus on one agent for use in a soundly designed clinical trial. For this purpose, we have selected divalproex sodium.

Divalproex sodium is a standard and commonly used anticonvulsant and mood stabilizing agent that appears to be the best choice of active drug for the proposed study. It is a compound comprised of sodium valproate and valproic acid. In 1963, valproic acid was recognized to have anti-seizure activity, and it was approved as an anti-epileptic drug in the U.S. in 1978. The divalproex formulation, which is an enteric-coated, stable equimolar combination of sodium valproate and valproic acid, became available in 1983. In 1994, it was shown to be superior to placebo and comparable to lithium in treating acutely manic bipolar patients, and the FDA approved it in 1995 for this indication. Also, it is used in conjunction with lithium or carbamazepine to prevent recurrent manic or depressive episodes during long-term treatment of bipolar disorder (PDR, 2006).

This line of research opens an exciting area of inquiry that can 1) characterize a treatable clinical population more specifically than ever before and, 2) potentially offer an effective and widely available treatment modality that can ease the fronto-limbic disinhibition symptoms of TBI resulting in a significant lessening of ethanol intake for the same purpose. Because ethanol self-treatment often leads to increasing ethanol tolerance and the subsequent symptoms of AA/D, specific treatment for those suffering affective lability after TBI can potentially prevent AA/D in vulnerable individuals. In addition, specific treatment may also ameliorate AA/D in cases where it has already occurred. If found effective, anticonvulsant treatment for the mood and anxiety symptoms resulting from TBI offers the possibility of altering an otherwise downhill natural course into alcohol dependence, potentially affecting the many thousands of persons who suffer affective instability after closed head TBI. If proven, this treatment may act in both preventive and curative capacities. Last, establishing a treatment effect in this area will shed light on possible interactions between affective lability and neuro-inhibition as these relate to basic mechanisms whereby the brain's vulnerability to alcohol addiction becomes manifest. In short, if this study can demonstrate a valid effect it will open further doors of inquiry.

Body

Recruitment

This report closes the second year of study funding. As it took substantial time locally to receive all approvals for this project, we began enrollment near the end of first year. For our initial efforts we targeted services and clinics at the Denver VA Medical Center (DVAMC) who regularly saw TBI patients. Dr. Beresford and Mr. Schmidt gave outreach presentations to the Substance Abuse Treatment Program (SATP), Mental Illness Research, Education and Clinical Center (MIRECC), Inpatient Psychiatry, Outpatient Mental Health Clinic, TBI Clinic personnel and others. At that time we also began generalized outreach, advertising the study throughout the DVAMC with flyers and brochures. We consented our first participant in October 2009. This was followed by the first subject to be randomized to the study drug trial in February 2010.

We continued our outreach efforts and in February our team spoke at the Mental Health Service meeting at the DVAMC. We continued to screen patients and enroll at a steady pace. By June 1st we had randomized 10 patients into the drug trial. During the summer we expanded our outreach beyond the DVAMC by running advertisements in a free local newspaper. Our staff also spoke with Operation TBI Freedom, a local organization dedicated to working with Veteran TBI patients.

While we have noticed some seasonal variation in study enrollment, as noted in the attached figures, we are on track for successful completion of the study. Figure 1 details our enrollment totals, notably in our experience entering 16% of those who contact us by phone and 52% of those whom we evaluate in person. These ranges are roughly what we anticipated. In Figure 2 we compare actual and projected enrollment. While above projected enrollment, there appeared to be a seasonal variation over the past summer. On further examination, we found a drop-off in phone screens meeting enrollment criteria (Figure 3). This suggested to us that we needed to widen our recruitment efforts. While the projections are on target we hope to recruit at a faster rate than projected and would like to finish recruitment as soon as possible.

In the coming year we plan to increase recruitment by several methods. First, we will utilize patient registries in the MIRECC and TBI clinics to inform potential participants of the study through direct mailings and clinic contacts. Second, we will target young OEF/OIF Veterans by advertising at local colleges and other locations frequented by young Veterans. Third, since May, Dr. Beresford has been running a medication clinic in the SATP. We expect this to lead to referrals as well. Our target for the coming year is to randomize two-thirds of the total complement of subjects, with intent to complete the randomization phase of the trial in the first six months of the following year.

Enhancing Enrollment

Reviewing our enrollment to this point, the majority of our subjects found the study through the SATP. Participant compliance has been remarkably high, with 92% (11/12) completing the protocol once randomized, well above the anticipated 50% dropout rate. Most subjects randomized to the drug trial did not miss a visit, and all but 2 completed all 10 weeks. We have lost 2 participants to incarceration, though neither was on medication phase at the time.

A second observation on enrollment is that throughout the first year of recruitment our participants were all over 40 years old. Many were in the military during the Vietnam War, while some were in active service in later years. One participant was deployed to both Dessert Storm and Operation Iraqi Freedom. While we are delighted with this response overall, we have begun to target the younger generation of Veterans who were deployed to Iraq and Afghanistan.

Young Veterans of Operation Enduring Freedom / Operation Iraqi Freedom (OEF/OIF) have been a challenging group to recruit. Consulting with researchers around the country we have learned that this is a common experience when trying to recruit this group into research studies. We began working with the intake clinic for OEF/OIF veterans at the DVAMC soon after starting enrollment. The clinic staff has been quite helpful, volunteering to give study information to any of their patients who screen positive for a TBI. While this has resulted in the clinic providing information to approximately 80 patients, only one has contacted study staff, and he eventually declined to join the study. This demonstrates the difficulty in recruiting young veterans. We have begun working with the DVAMC Public Affairs Office and the Medical Media Office to design and execute an age-specific, COMIRB/VA approved media campaign targeting the current cohort of returning Veterans.

Pilot Investigations

In working with this group of patients we have noticed several patterns emerging that offer new avenues of potential investigation.

1) Do alcohol and TBI contribute independently to brain sub-structure volume changes?

We have now acquired MRI scan data on 13 subjects. Internal review of these scans by Dr.'s Beresford and Wortzel suggest changes to brain structure beyond what would normally have been expected from an alcohol abusing cohort alone. We plan now to work with Dr. Davatzikos to compare these scans against MRI data from both a) a pre-existing group of alcoholics with no history of head injury as well as b) a normal control group. These groups will be matched for age and gender, and will allow us to investigate the extent to which head injury affects the structural changes that occur in the brain over and above those expected from alcohol abuse. Brain volume comparisons will be made, including automated measures of brain sub-structure volumes (Beresford et al, 2006).

2) Is there a stimulant abusing TBI sub-population better treated with antidepressants?

As we've reviewed our screen fails and continue to work with this population, a subset of TBI patients appears to prefer stimulants as opposed to sedating agents such as alcohol. We have begun to wonder if treatment with an antidepressant would benefit this group. We will review this concept with our expert consultants in brain injury, Dr. Arciniegas and Dr. Kelly.

3) Can we separate components of PTSD and TBI in this population?

Additionally, a large number our participants report Post-traumatic Stress Disorder (PTSD) symptoms (see Figure 4), with increasing numbers among the OEF/OIF cohort. Some patients report experiencing traumatic events at the time their head injury occurred. Others report traumatic events unrelated to their TBI. Regardless of the source of the trauma, it is often difficult to differentiate symptoms of PTSD and symptoms of TBI. In consultation with our inpatient PTSD unit, we have begun to explore a comparison of TBI patients with and without PTSD and the resulting treatment differences.

Key Research Accomplishments

At this stage of the investigation the study continues to compile and store research data. According to study design we have not yet begun to analyze these data with respect to the study hypotheses. We anticipate that a mid-enrollment review by James Murphy, Ph.D., the study

Data Safety Monitor, will occur sometime in the coming year. Unless those data suggest an overwhelmingly positive or negative effect of the active drug, we anticipate elucidating principal research accomplishments once enrollment is complete, the study blind is broken and we analyze the data.

Reportable Outcomes

Dr. Beresford presented an abstract, poster and oral presentation based on the preliminary study to the Military Health Research Forum held in Kansas City, MO, on August 31, 2009.

Conclusion

Any conclusions will occur after data collection and analysis.

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Appendix

Figure 1:

Enrollment Log

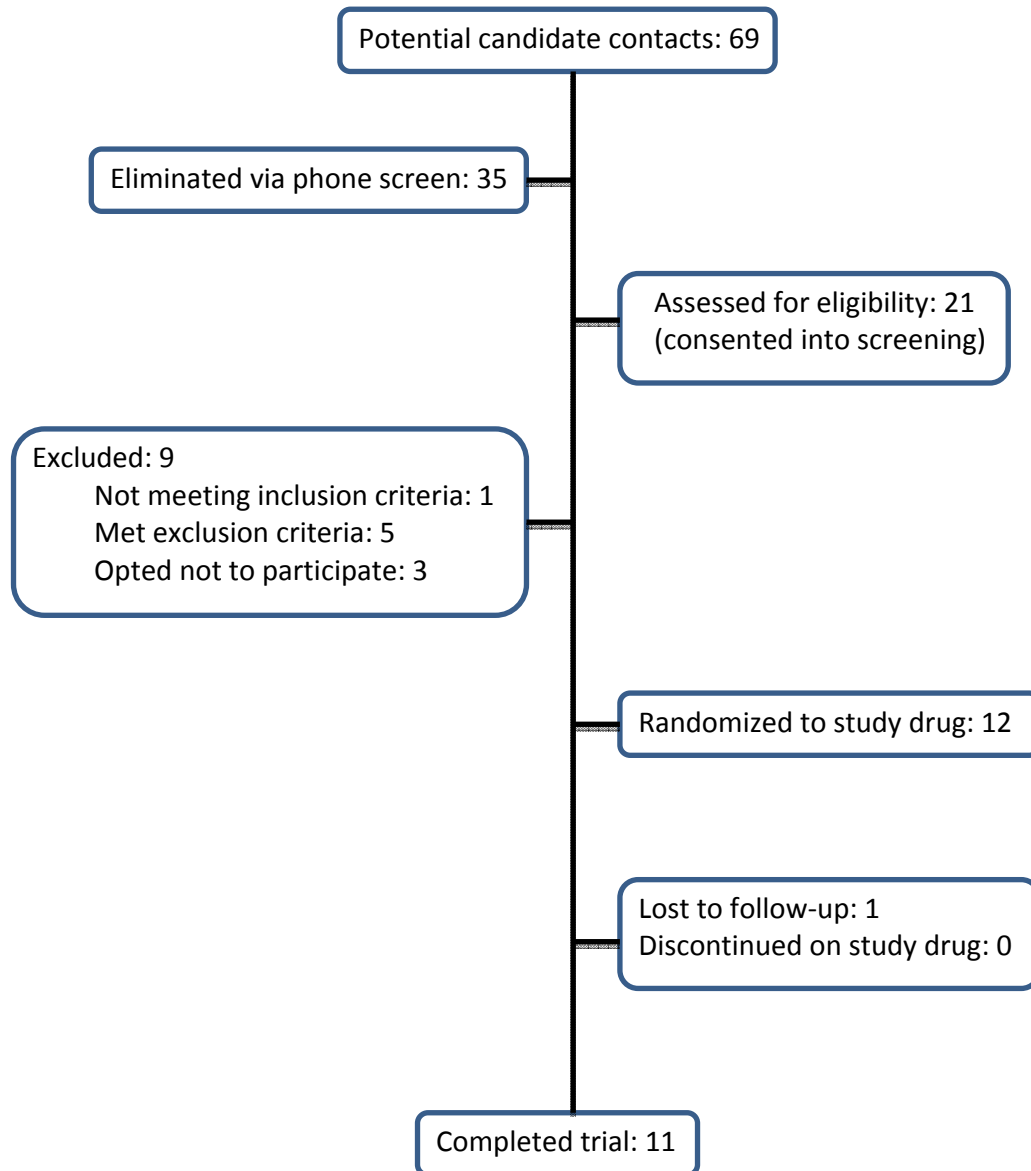


Figure 2:

Exposure to Study Drug

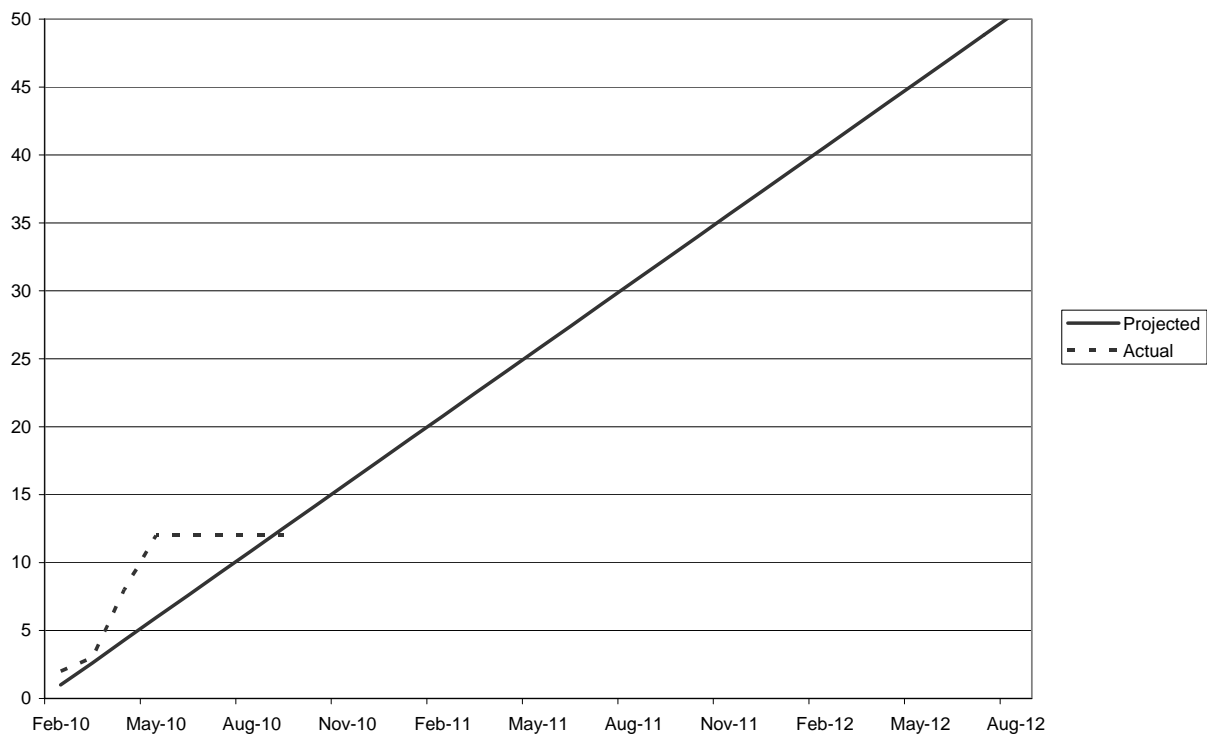


Figure 3:

Percent Meeting Screening Criteria

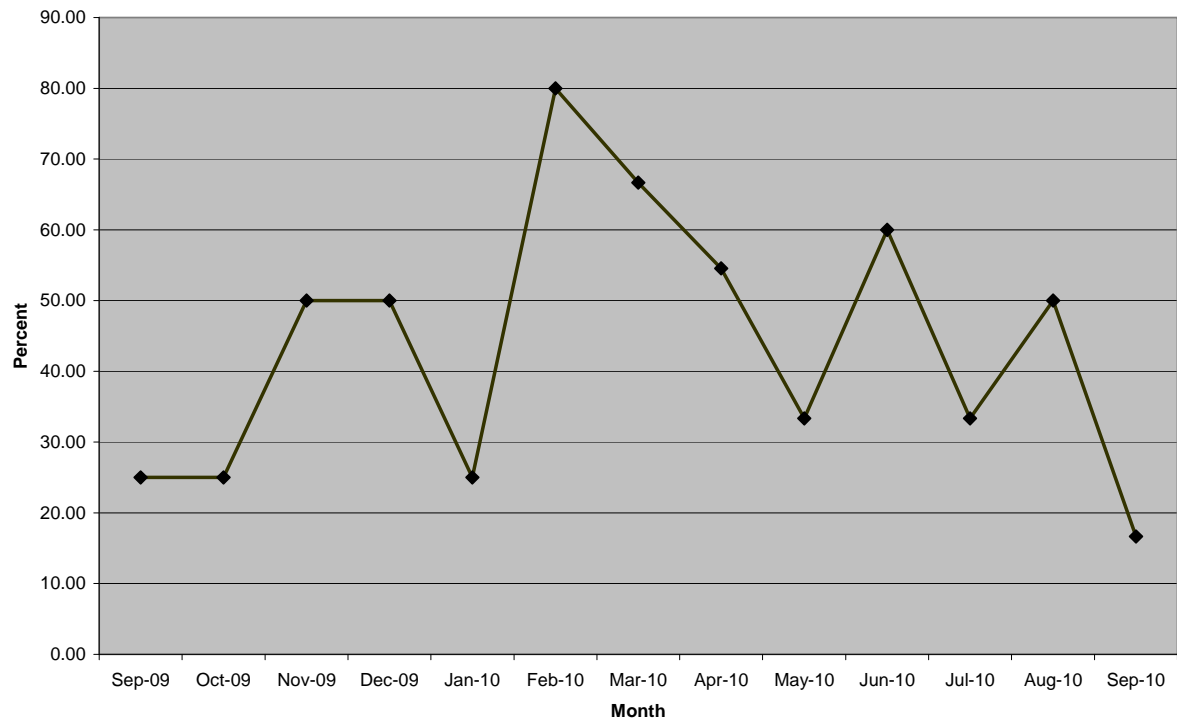


Figure 4:

TBI Alone vs TBI & PTSD

	PTSD + TBI	TBI Alone
Evaluated	3	5
Randomized	3	8
Total	6	13